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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,661	07/20/2000	Marcel Linschoten	1103326 0631	9121

7470 7590 07/10/2003

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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 07/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/600,661	LINSCHOTEN ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 12-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 12-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1&5&11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to an election filed on 5/27/03. There are twenty-six claims pending. Claims 1-5 and 18 are compound claims. Claim 9, 13, 14, and 26 are is a composition claim. Claims 12, 16, and 17 are use claims. Claims 6-8, 19-25, and 28 are synthesis claims. Claims 15 and 27 concern a kit. The application concerns some pyridine mercapto carboxylic acid compounds, compositions, and uses thereof.

2. Applicants' comments about claims 10 and 11 are noted. These two claims were mistakenly included in the listed claims in the restriction requirement of paper #9. These two claims have, in fact, been canceled previously. The Examiner regrets the error.

3. Applicants' comments about substituted pyridine compounds are noted. Two indefiniteness rejections regarding this issue are made below.

Election/Restrictions

4. Applicant's election of Group II in Paper No. 10 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

5. Objection is made to claims 1-9 and 11-28 as containing non-elected subject matter. The claimed compounds, compositions, and methods that employ them

present a variable core. Formula I contains compounds drawn to the non-elected inventions to the extent it reads on compounds other than R_1 = pyridyl.

Title

6. The title of the invention is not descriptive after restriction. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: insertion of the phrase "Pyridine Mercapto Carboxylic Acid" at the beginning of the title.

Specification

7. The incorporation of essential material in the specification by reference to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973). In lines 6-7, page 16 Applicants refer to two *in vitro* tests used to assay their compounds in lines 19-24, page 18. This data goes to the heart of possible enablement for their therapeutic claims.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 12-17, and 19-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In line 24, page 6 Applicants' define "heterocyclyl" as substituted or unsubstituted. Substituted by what? The plain meaning of heterocyclyl, for example pyridyl, would be a C_5H_4N radical attached to radical X at either the 2, 3, or 4 position. The claims measure the invention. The U.S. Court of Customs and Patent Appeals wrote *In re Priest*, 199 USPQ 11 "We have consistently held that no applicant should have limitations of the specification read into a claim where no express statement of the limitation is included in the claim." *In re Prater*, 56 CCPA 1381, 1396, 415 F.2d 1393, 1405, 162 USPQ 541, 551 (1969)." The Examiner suggests adding the specific substituents desired, being mindful of not adding new matter.

9. Claim 18 recites the limitation "wherein the basic group is selected from the group consisting of amino, amido, and guanidino" in lines 2 and 3. There is no antecedent basis for this limitation in the claim 1 upon which this claim depends. Claim 1 refers to basic groups but only upon the non-elected alkyl, cycloalkyl, oxygen and sulfur, heterocyclyl, and aryl groups. The punctuation in claim 1

makes clear that such groups are not attached to the basic nitrogen-containing heterocyclyl radicals.

10. Claims 1-9, 12-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "a carboxylic acid isostere" is indefinite. Lines 29-30, page 5 list the chemical property this radical possesses but does not give its structure. The Examiner understands that the six radicals listed in the preceding line are sometimes referred to as isosteres of carboxylic acids but presumably Applicant is intended to claim even more radicals as R_3. What are their structures?

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12, 13, 16, and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for preventing diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants are not enabled for preventing any of these diseases. The only established prophylactics are vaccines

not the pyridine mercapto carboxylic acid compounds such as present here. In addition, it is presumed that "prevention" of the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art, and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. 1) As discussed above, preventing diseases requires identifying those patients who will acquire the disease before cardiovascular disease occurs. This would require extensive and potentially opened ended clinical research on healthy subjects. 2) The passage spanning line 1, page 17 to line 5, page 18 lists the diseases Applicant intend to treat. 3) There is no working example of such a preventive procedure in man or animal in the specification. 4) The claims rejected are drawn to clinical cardiovascular medicine and are therefore physiological in nature. 5) The state of the art is that no general procedure is art-recognized for

determining which patients generally will become diseased before the fact. 6) The artisan using Applicants invention would be a Board Certified physician in cardiology with an MD degree and several years of experience. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of cardiovascular diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent cardiovascular generally. 7) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). 8) The claims broadly read on all patients, not just those undergoing cardiovascular therapy and on the multitude of compounds embraced by Formula (I).

The Examiner suggests deletion of the word "prophylaxis" and the phrase "susceptible to".

12. Claims 12, 13, 16, and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for treating "conditions associated with inhibition of carboxypeptidase U". The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized above. a) Determining if any particular claimed compound would treat any particular carboxypeptidase U associated disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different diseases described below, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large degree of experimentation. b) The direction concerning treating carboxypeptidase U diseases is found in the passage spanning line 1, page 17 to line 5, page 18, which merely states Applicants' intention to do so. Applicants describe formulations in the passage spanning line 7, page 15 to line 23, page 16. Doses required to practice their invention are taught in lines 25-29, page 16. A 10,000-fold range of doses is proposed. Since no carboxypeptidase U inhibitor has ever been used to treat any human disease, how is the skilled physician to know what dose to use for each of these different diseases? Since no testing data is provided how is this dose

to be calculated? There is an *in vitro* assay mentioned in lines 19-24, page 18. No details are provided and it is not possible to determine what is this assay. No data is provided and it is unclear if this assay is correlated to clinical treatment of any human diseases. c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of disease, which involves physiological activity. e) The state of the clinical arts in carboxypeptidase U related diseases is provided by Boffa (Curr Drug Targets) who clarifies the speculative nature of clinical uses of such inhibitors in the last line of the abstract.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

h) The scope of the claims involves all of the thousands of compounds of claim 1 as well as the unknown list of diseases embraced by the term "conditions associated with inhibition of carboxypeptidase U". Thus, the scope of claims is very broad.

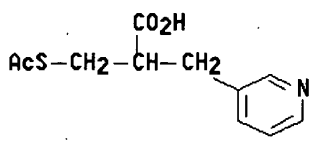
MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 102

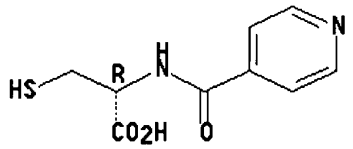
13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

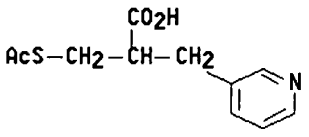
Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Mimura (JP 01254654 A2, CA document). The compound shown below fits formula (I) with R_1 = 2-pyridyl, X = $C(Z)_2$, R_2 = R_5 = Z = hydrogen, R_3 = CO_2H, Y = CH_2, and R_4 = S-CO-methyl. It has Registry Number 126772-54-1. The 3-pyridyl and 4-pyridyl compounds are also found in the abstract.



14. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Agfa-Gevaert (DE 3838467 A1, cited by Applicants). The compound shown below fits the limitations of Formula (I) with R_1 = 4-pyridyl, X = CONH, R_2 = R_5 = Z = hydrogen, R_3 = CO_2H, Y = CH_2, and R_4 = SH. It is found in line 38, page 2 of the reference. It is Example 6 and the 2-pyridyl compound is Example 7.



15. Claims 1-6 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Norcini ('259). The compound shown below fits formula (I) with R_1 = 3-pyridyl, X = $C(Z)_2$, R_2 = R_5 = Z = hydrogen, R_3 = CO_2H, Y = CH_2, and R_4 = S-CO-methyl. It has Registry Number 123986-61-8. It is found in lines 39-54, column 8 of the reference. The process of making taught in this reference uses a compound of Formula VI with the radicals defined as above and thioacetic acid. Thioacetic acid fits Formula (IX) with R_5 = acetate. Thus, claim 19 is anticipated.



Allowable Subject Matter

16. Claims 7-9, 14, 15, and 18-28 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Conclusion

17. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for before final amendments is (703) 872-9306. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Thomas McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK
July 3, 2003